

IN THE SPECIFICATION:

Please amend the specification as follows:

Please add the following subheading and paragraph on the first page after the Title of the Invention:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a national phase entry under 35 U.S.C. § 371 of International Patent Application No. PCT/NL01/00079, filed February 9, 2000, published in English as International Patent Publication WO 00/48003 on August 17, 2000, which claims priority to European Patent Application No. EP 99200391.3, filed February 11, 1999.

Please replace the paragraph on page 2, lines 1-11, with the following paragraph:

Brain homogenates from cows with BSE produce, after inoculation of mice, a characteristic pattern of brain lesions in mice. Also, characteristic incubation periods in inbred lines of mice are seen. This is identical to the pattern elicited by brain tissue from individuals who recently have died from new-variant Creutzfeldt-Jakob disease (nvCJD; Bruce, 1997). The conclusion is that the BSE agent is identical to the nvCJD agent. ~~Up to now~~ Through 1996, this variant has caused the death of 35 young Britons and one Frenchman (Will *et al.*, 1996; ~~info: CJD Statistics per 30 November 1998, Internet~~).

Please replace the paragraph on page 7, lines 20-32, with the following paragraph:

ELISA systems were designed for detection of PrP<sup>Sc</sup>, isolated from brains of scrapie-affected mice and hamsters (Kascsak *et al.*, 1987) and PrP<sup>Sc</sup> from murine brain and spleen (Grathwohl *et al.*, 1997). In these assays, the PrP<sup>C</sup> fraction was beforehand removed by PK-treatment and the purified and ~~solubilised~~ solubilized analyte was directly coated onto the microtiter plate. ~~Solubilisation~~ Solubilization of PrP<sup>Sc</sup> was by treatment with SDS or extraction with 77% formic acid, drying and resuspension in buffer (Kascsak *et al.* 1987). The denaturing action of formic acid was found to enhance the antibody response to PrP<sup>Sc</sup> considerably compared to ~~untreated~~ untreated or SDS-treated material. In this ELISA rabbit antiserum to the mouse scrapie strain ME7 PrP<sup>Sc</sup> was used.

Please replace the paragraph starting on page 8, line 25 to page 9, line 3, with the following paragraph:

A sandwich type of ELISA was used to monitor the bioproduction of recombinant hamster PrP<sub>(90-231)</sub>, the protease resistant core of PrP<sup>Sc</sup> (Mehlhorn *et al.*, 1996). As a capture antibody the Fab fragment of mAb 3F4 was coated onto the microtiter plate. This antibody was raised against hamster scrapie strain 263K and reacts with hamster, human and feline PrP. As the second antibody mAb 13A5 (to scrapie hamster PrP<sup>Sc</sup>) was used. Samples from the different stages of purification were measured in this ELISA. However, the practical conditions under which PrP<sup>Sc</sup>, in order to be detected as an antigen, is brought into an unfolded state by chaotropic agents like 3-4 gdnSCN, are not compatible with the immunochemistry of a sandwich type of ELISA.

Please replace the paragraph starting on page 19, lines 8-28, with the following paragraph:

Further more, the invention provides a method further comprising treating at least one first sample with gdnSCN or a functional equivalent thereof and leaving at least one second sample untreated with gdnSCN or a functional equivalent thereof and comparing the test results of ~~said the~~ first sample with ~~said the~~ second sample. We can, for example, discriminate between TSE-positive and negative cases after duplicate dot blotting of extracts of brain tissue onto a membrane. Extraction is in detergent-containing (lysis) buffer. One aliquot is left untreated and the other one is treated in 4 M gdnSCN (~~Figure FIG.~~ 3) or, after PK-digestion, treated with 4 M gdnSCN (~~Figure FIG.~~ 4). Then, after immunostaining, the treated sample is compared to the untreated sample. The signal of the normal protein (PrP<sup>C</sup>) is greatly reduced or retains the same intensity upon treatment and can be further reduced by protease K digestion. In this way comparison of untreated and treated samples leads to a decrease or no increase of signal ~~of in~~ samples from normal individuals, but ~~t to~~ a significant increase of signal ~~of in~~ samples from TSE-affected animals. By this dual internal control, the discriminating value of the test is considerably ~~enforced~~ reinforced.

Please replace the paragraph on page 33, lines 29-32, with the following paragraph:

- Safar, JJ., H. Wille, V. Itri, D. Groth, H. Serban, M. Torchia, F.E. Cohen & S.B. Prusiner (1998). Eight prion strains have PrP<sup>Sc</sup> molecules with different conformations. *Nature Medicine* 4(10):1157-1165.